

# **EXHIBIT 2**

**IN THE UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

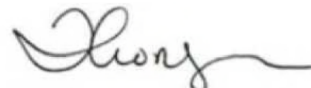
**IN RE JOHNSON & JOHNSON  
TALCUM POWDER PRODUCTS  
MARKETING, SALES PRACTICES, AND  
PRODUCTS LIABILITY LITIGATION**

**MDL NO. 16-2738**

***THIS DOCUMENT RELATES TO:  
Newsome, et al. v. Johnson & Johnson, et al.  
3:18-cv-17146***

**RULE 26 EXPERT REPORT OF  
TERI LONGACRE, MD**

Date: May 28, 2024



Teri Longacre, MD

## **I. BACKGROUND AND QUALIFICATIONS**

I am a board-certified diagnostic surgical pathologist at Stanford Medicine with subspecialty expertise in gynecologic pathology. I received my medical degree in 1985 from the University of New Mexico School of Medicine in Albuquerque, New Mexico, where I completed my residency training in anatomic and clinical pathology. Following residency, I completed a fellowship in surgical pathology at Stanford University. Thereafter, I took a position as Assistant Professor at Stanford University and rose through the ranks of the professoriate to my current position as Professor of Pathology. I am the Emerita Richard L. Kempson Endowed Chair in Surgical Pathology at Stanford University School of Medicine, where I serve as Director of Gynecologic Pathology and Director of the ACGME-approved fellowship in Gynecologic Pathology, a program I founded in 2007. In addition, I am the Director of Gastrointestinal Pathology and Director of the ACGME-approved fellowship in Gastrointestinal Pathology, a program I also founded in 2013. I am the former Director of the Stanford Hospital Tissue Committee and a former member of the Stanford Care Improvement Committee, which oversees the quality of patient care in the hospital. In addition to many other extramural committee appointments, I am a former President of the Association of Directors of Anatomic and Surgical Pathology, in part due to my prior work as a Director of Surgical Pathology at Stanford.

I have internationally recognized expertise in benign and cancerous conditions of the female reproductive system, including cancers of the ovary, uterus, cervix, vagina and vulva, and have published extensively in the peer-reviewed medical literature on gynecologic pathology. I provide continuing medical educational lectures on gynecologic pathology to practicing pathologists regionally, nationally and internationally, and have authored and co-authored numerous review articles, book chapters and a textbook in gynecologic pathology. I also provide annual resident and fellow lectures at Stanford Medicine in the areas of non-neoplastic and neoplastic gynecologic pathology and examine gynecologic pathology specimens, including ovarian cancer specimens, on a routine basis. I have published and lectured extensively on the topic of ovarian cancer pathology. Because of my expertise in gynecologic pathology, I was invited to become a member of the American Board of Pathology Test Committee, which provides gynecologic pathology questions for the certification exam for pathology residents and for the maintenance of certification exam for practicing pathologists. I co-authored the 4th edition of the World Health Organization (WHO) Breast and Gynecologic Tumours, and am an expert editor and co-author of the 5th edition of the WHO Classification of Tumours: Female Genital Tumours. I am also editor of the 7<sup>th</sup> edition of Sternberg's Diagnostic Surgical Pathology and associate editor of the chapters on gynecologic pathology in that book. I am a member of a number of pathology societies and editorial boards, a list of which is provided in the attached curriculum vitae (Exhibit A), which also sets out my education and training in detail and lists my peer-reviewed publications, committee appointments, invited lectures and active grant funding.

My clinical diagnostic activities chiefly include examination of surgical gynecologic and gastrointestinal specimens, including small biopsies and large organ resections. My annual case volume amounts to 5,000 to 7,500 cases; one-half to one-third are gynecological cases and of those, twenty to thirty percent are ovarian cancer cases. In addition to anatomic pathology, I am board certified in clinical pathology, which enables me to integrate findings in the areas of chemistry, hematology, microbiology, immunology, molecular pathology and other special laboratory studies as they relate to my practice of gynecologic pathology. In this capacity, I

routinely provide clinical and pathologic consultations to physicians at Stanford Medicine; this entails macroscopic (gross) and microscopic review of surgical pathology specimens and review of relevant clinical information to render informed patient diagnoses. I am a regular participant in the Stanford Gynecologic Oncology Interdisciplinary Tumor Board as well as several Gastrointestinal Tumor Boards. In addition to the clinical work I provide for Stanford patients, I also receive requests for my consultative opinion from both pathologists and treating physicians regionally, nationally, and internationally.

My opinions are held to a reasonable degree of medical and scientific certainty and are based on my education, training and experience, as well as my clinical and scientific research, general knowledge of the literature, my pathologic review of thousands of ovarian cancer cases throughout my career, and my review of the relevant medical records and pathology in this case. I reserve the right to amend or supplement my opinions, if additional, relevant information becomes available to me. The references and attached materials list (Exhibit B) include many sources that I have considered in forming my opinions; of course, it is impossible for me to identify here all sources of information I have considered over the many years of my career.

I am compensated at a rate of \$600 per hour for consulting on this case.

## **II. OVARIAN CANCER**

Ovarian cancer is not a single disease. It comprises a set of distinct cancers, each of which exhibits different clinical, histological, epidemiological, and molecular underpinnings. Ovarian cancer can be separated in to two broad groups: epithelial ovarian cancer and non-epithelial ovarian cancer (e.g., germ cell, sex-cord stromal tumors), as well as a variety of miscellaneous tumors and metastases. The plaintiffs' expert reports focus on epithelial ovarian cancer, and not any other type of ovarian cancer.

### **A. Epithelial Ovarian Cancer (EOC)**

Epithelial ovarian cancer (EOC) is the most common type of ovarian cancer and is comprised of multiple, distinct diseases, including high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), mucinous carcinoma, endometrioid carcinoma, clear cell carcinoma, and other rare subtypes.

HGSC is, by far, the most common type of EOC. These tumors arise from tubal-type epithelium, usually in the fallopian fimbria and, less commonly, on the ovarian surface or within ovarian epithelial inclusion cysts. For those that arise on the ovarian surface or within inclusion cysts, the current belief is that these result from deposition of fallopian tube epithelium that subsequently undergoes transformation at these sites. Nearly every HGSC, including precursor lesions, harbors a deleterious mutation in the *TP53* tumor suppressor gene, which is considered to be one the earliest known molecular events in the development of HGSC (Ahmed 2010; Vang 2016). In addition, HGSC are deficient in homologous recombination and lack the ability to repair double strand DNA breaks. About 10% to 12% of women with HGSC carry germline mutations in the *BRCA1* or *BRCA2* genes. An additional, smaller percent of HGSC occur in association with germline mutations in other homologous recombination genes (Song 2014). Additional genes that have been associated with hereditary ovarian cancer include the tumor suppressor gene, *TP53*, in

the Li-Fraumeni syndrome, as well as several other genes involved in the double-strand breaks repair system, such as *CHEK2*, *RAD51C*, *RAD51D*, *RAD50*, *BARD1*, *BRIP1*, *MRE11A*, and *PALB2* (Madariaga 2019). Recent literature suggests that close to 25% of ovarian cancers are associated with germline mutations, and of these, 29% have mutations in genes other than *BRCA1* or *BRCA2*. (Frey 2017). Other patients may have a clear familial predisposition to developing ovarian carcinoma for as yet unknown reasons. The *BRCA1/2*, *CHEK2*, *RAD51*, *BRIP1*, *BARD1*, *MRE11A*, and *PALB2* genes encode proteins that play a critical role in maintaining genomic stability by promoting error-free DNA repair. (Gudmundsdottir 2006; Toss 2015). Approximately one-third of sporadic HGSC may also contain somatic *BRCA1* or *BRCA2* mutations, *BRCA1* methylation, or genomic aberrations in these other homologous recombination genes. (Madariaga 2019).

Ovarian cancers associated with homologous recombination defects exhibit a series of characteristic morphologies. Most are HGSC with marked nuclear pleomorphism with giant bizarre nuclei and high mitotic index (Fujiwara 2012; Soslow 2012). They also tend to show a solid, pseudoendometrioid, or transitional cell carcinoma-like (“SET”) morphology (Soslow 2012). When T-cell subtypes are examined, *BRCA1/2*-mutated tumors exhibit significantly increased CD3+ and CD8+ tumor infiltrating lymphocytes, as well as elevated expression of PD-1 and PD-L1 in tumor-associated immune cells compared to homologous recombination-proficient tumors. Women with *BRCA1/2*-mutated HGSC tend to have a better overall prognosis and response to chemotherapy (particularly PARP-inhibitors) than women with non *BRCA1/2*-mutated HGSC (Dann 2012).

It is now well established that a significant majority of so-called “ovarian” HGSC arise from the distal fimbrial end of the fallopian tube from a precursor lesion known as serous tubal intraepithelial carcinoma (STIC). Criteria for site-assignment in extrauterine HGSC have been proposed (Singh 2015; McCluggage 2015; Singh 2014; Singh 2016; Singh 2016b) and the use of these criteria result in a high-proportion of previously presumed “ovarian” HGSC (approximately 80%) being classified as tubal in origin, while primary peritoneal HGSC are exceedingly rare. A diagnosis of primary peritoneal HGSC should only be made when there is no ovarian parenchymal HGSC and no mucosal STIC or HGSC within either tube, both of which should be grossly visible in their entirety and histologically examined in total using a SEE-FIM protocol.

Clinically, HGSC are aggressive tumors that primarily affect older women (median age at diagnosis is 63) (SEER Cancer Stat Facts: Ovarian Cancer, 2024). Most patients (75%) who develop HGSC present in advanced stage (FIGO III-IV), and there is no currently accepted approach to reduce mortality through early detection (Goff 2000; Hogg 2004). The 5-year survival of women with advanced stage disease is about 20% compared with 80-90% for those with FIGO stage I-II disease. While HGSC often responds to standard platinum-based chemotherapy, prevention strategies have largely been through surgery: prophylactic and risk-reduction salpingo-oophorectomy in women who are at elevated risk, such as those with germline *BRCA* mutations or strong family cancer histories (Kauff 2002). Prophylactic salpingo-oophorectomy reduces the risk of *BRCA*-related gynecologic cancer by 96% (Haber 2002). Although the risk of ovarian cancer is diminished, there remains a small risk (0.8-1%) of subsequently developing a peritoneal HGSC, especially in women who have mutations in the *BRCA1* and *BRCA2* genes (Casey 2005). Oral contraception use appears to reduce the risk of HGSC, as do number of term pregnancies and breastfeeding. The protective effects of these apparent diverse risk-reducing factors is attributed

to interruption of ovulation and hence, decreased proliferation of the tubal epithelial cells now believed to be involved in the development of HGSC. A recent study that demonstrated tubal ligation results in decreased proliferation of the progenitor cells in the distal fallopian tube corroborates this theory (Tiourin 2015).

HGSC is now believed to be distinct from low-grade serous carcinoma (LGSC). Except for their shared morphologic resemblance to tubal-type epithelial cells, HGSC and LGSC differ in genetic abnormalities, pathways of tumorigenesis and clinical behavior. Whereas HGSC is an aggressive tumor affecting older women, the clinical course of LGSC is typically more prolonged, with LGSC typically affecting women of somewhat younger age. LGSC is more refractory to chemotherapy than HGSC, probably because of the lower proliferative rate of the former. LGSC arises by step-wise progression from benign through borderline to malignant tumors, while most HGSC arises *de novo* in the fallopian tube. While HGSC commonly shows mutations in *TP53* and *BRCA1* or *BRCA2*, LGSC is more likely to have mutations in *BRAF*, *KRAS*, and *NRAS* (Romero 2020). Women with germline *BRCA* mutations are at increased risk of HGSC, but not of serous borderline tumor or LGSC, further underscoring differences in pathogenesis between HGSC and LGSC. LGSC is not associated with mutations in homologous recombination genes. The histologic distinction between HGSC and LGSC is based primarily on nuclear features, with less than three-fold variation in nuclear size in LGSC. A secondary diagnostic criterion is mitotic activity, LGSC having less than 12 MF/10 HPF. There are also differences in architectural features between LGSC and HGSC, with micropapillary architecture and psammoma bodies more common in the former, while HGSC frequently shows solid growth pattern, at least focally, which is an uncommon feature in LGSC. With the exception of p53, immunohistochemistry is not particularly helpful (and is seldom required) to separate LGSC and HGSC.

In contrast to HGSC, endometriosis is a well-recognized precursor of ovarian endometrioid carcinoma and clear cell carcinoma. At least 25% of ovarian endometrioid carcinomas will have foci of concomitant endometriosis on pathologic examination, while up to 47% of clear cell carcinomas have foci of concomitant ovarian endometriosis on pathologic examination and up to 68% have concomitant endometriosis in the pelvis (Fadare 2019). Accordingly, when endometriosis is found in the overall specimen, pathologists regard this as compelling evidence of an origin from endometriosis, even in the absence of a demonstrable transition from endometriosis. Endometriosis is commonly associated with adenomyosis in the uterus; an MRI study documented a prevalence of endometriosis in the setting of adenomyosis of 80.6% and a prevalence of adenomyosis in the setting of endometriosis of 91.1% (Zannoni 2020; Leyendecker 2015). Data from RNA transcriptional and DNA methylation analyses suggest differences in menstrual cell cycle state (e.g., proliferative or secretory) of endometrial progenitor cells may account for the different cellular phenotypes and clinical behaviors of endometrioid and clear cell carcinomas (Beddows 2024).

Endometrioid carcinomas exhibit morphologic features that resemble uterine endometrial carcinoma and are graded similarly (i.e., FIGO grade 1, 2 or 3), depending on the degree of glandular differentiation and the presence of cytologic atypia. Like their uterine counterparts, they often exhibit foci of squamous metaplasia. They harbor mutations similar to those seen in the uterine corpus (*PTEN*, *PIK3AC*, *CTTNB1*, *ARID1A*). Mutations in *TP53* are uncommon (no more than 11%-24%), particularly in the lower grade tumors, and they are not associated with genomic aberrations in homologous recombination genes. Endometrioid ovarian carcinomas often express

the receptors for estrogen and progesterone. Mismatch repair protein deficiency can be seen in almost 20% of tumors and 3%-10% harbor mutations in *POLE*. Up to 30% of ovarian endometrioid carcinomas are associated with endometrioid endometrial carcinoma (Romero 2020). A family history of ovarian endometrioid cancer in a first-degree relative, or any ovarian cancer, has been associated with an increased risk of ovarian endometrioid cancer, with relative risks that range from 2.81 to 3.81 (Fadare 2019).

Clear cell carcinomas have a distinct appearance characterized by clear or eosinophilic cells arranged in papillae, cysts, and solid nests. They are not graded. Like endometrioid carcinomas of the ovary, they are not associated with genomic aberrations in homologous recombination genes. Like ovarian endometrioid carcinoma, ovarian clear cell carcinoma may be associated with mutations in *ARID1A*, which is currently considered an early molecular event when these tumors arise from endometriosis. Other gene mutations include *PIK3AC*, *KRAS*, and *PPP2R1a*. Mutations in *TP53* are uncommon (no more than 20%) (Romero 2020). Clear cell carcinomas typically do not express receptors for estrogen and progesterone. Like ovarian endometrioid carcinoma, ovarian clear cell carcinoma may be associated with mutations in genes that encode DNA mismatch repair proteins (Bennett 2016). These mutations may be somatic or germline. Germline mutations in these genes are seen in patients with Lynch syndrome, a hereditary cancer syndrome that is associated with increased risk of developing carcinomas in the uterine corpus, ovary, colon, and renal pelvis, as well as a variety of other organs. Approximately 11% of all ovarian carcinomas arise in women with Lynch syndrome; most of these are endometrioid, clear cell, or undifferentiated.

Ovarian mucinous carcinoma is uncommon; because of the identification of a background teratoma or Brenner tumor in some cases, an ovarian teratoma or Brenner tumor has been considered a possible precursor (Simons 2020). Ovarian mucinous carcinoma is typically unilateral and low stage. Many of these tumors arise in the background of a mucinous borderline tumor. When recurrences occur, they do so early. Response to standard chemotherapy is poor. *HER2* amplification and overexpression is present in approximately 16% of cases, and targeted therapy against *HER2* has been proposed for use in these cases. Ovarian mucinous carcinoma is typically not associated with mutations in homologous recombination genes or DNA mismatch repair genes. The most common gene mutations are *CDKN2A* (76%), followed by *KRAS* (64%) and *TP53* (64%), and less commonly, *BRAF*, *PIK3CA* and *ARID1A* (Romero 2020).

Carcinosarcoma contains malignant epithelial and malignant mesenchymal elements, each of which are derived from the same clonal origin. The epithelial component is usually high grade and most often resembles serous or endometrioid carcinoma, but malignant mucinous, squamous, or clear cell elements or undifferentiated carcinoma, including small cell carcinoma of the pulmonary type, may be encountered as well. The mesenchymal component may have the features of a fibrosarcoma, leiomyosarcoma, endometrioid stromal sarcoma, or nonspecific sarcoma, or, in heterologous tumors, a rhabdomyosarcoma, chondrosarcoma, or osteosarcoma. Intracellular and extracellular hyaline droplets, which are PAS-positive, may be present in the sarcomatous and sometimes in the carcinomatous component. Carcinosarcomas develop most often in postmenopausal women (del Carmen 2012). They often harbor mutations in *TP53*.

Mesonephric-like carcinoma is a recently recognized tumor that exhibits morphological and immunophenotypic features suggestive of mesonephric adenocarcinoma, but is not anatomically associated with mesonephric remnants (Pors 2021). Ovarian mesonephric-like carcinomas exhibit

variable histologic patterns including glandular, tubular, papillary, and solid growth. Some cases show intraluminal eosinophilic colloid-like material. These tumors are diffusely positive for PAX8, but negative for ER and PR. GATA3 and TTF1 are both diffusely positive in these tumors. Mutations in *KRAS*, *NRAS*, *BRAF*, *CTNNB1* and/or *PTEN* have been identified in these tumors, supporting Mullerian epithelial derivation. They do not harbor mutations in *TP53*. Although data are limited, they appear to be clinically aggressive and are currently not graded.

Undifferentiated carcinoma exhibits no or only rare and minor foci of epithelial differentiation (Bennett 2021). Less than 5% of ovarian carcinomas are undifferentiated. A subset is associated with Lynch syndrome.

Mixed carcinomas account for less than 3% of ovarian carcinomas and most commonly consist of admixtures of endometrioid and clear cell carcinoma (Ye 2014)), often arising in association with endometriosis or endometrioid and undifferentiated carcinoma (so-called de-differentiated carcinoma).

In addition to the carcinomas described above, there exists a set of serous and mucinous borderline tumors in the ovary.

Serous borderline tumors (SBT) account for the vast majority of all ovarian borderline epithelial neoplasms and comprise approximately 15% of all ovarian serous neoplasms (Vang 2020). SBT is encountered most often between the ages of 30 and 60 years, whereas serous carcinomas are most common between the ages of 40 and 70 years. SBT is typically bilateral and has the capacity for extra-ovarian spread, recurrence, and death, even though the tempo of disease progression is significantly more indolent when compared to LGSC. The molecular profile of mRNA gene expression patterns is significantly different for SBT and LGSC versus HGSC (Gilks 1998), as is the pattern of genetic alterations, e.g., the presence of point mutations in *BRAF* or *KRAS* is more frequently associated with SBT and LGSC, while *TP53* mutation and somatic or germline abnormalities in *BRCA1* and/or *BRCA2* are more frequently associated with HGSC. SBT are composed of architecturally complex branching papillary and micropapillary structures not unlike that of LGSC, but they do not feature destructive invasion of the ovarian stroma. The nuclei are uniform or mildly atypical and mitotic activity is low. Atypical mitotic figures are absent. Transformation to LGSC occurs in at least 7% of women with SBT, occasionally decades after initial diagnosis. Transformation is associated with increased tempo of disease and a significantly more aggressive disease course with approximately 40-50% overall survival. In some instances, transformation is preceded by several recurrences of SBT, which may or may not exhibit increasing degrees of atypical proliferation. In other cases, the transformation appears at the time of first recurrence. Most transformations occur in the omentum, followed by intraabdominal or axillary lymph nodes (Longacre 2005). Very rarely, SBT transforms to a high-grade carcinoma.

Mucinous borderline tumors are composed of enteric-type epithelium (gastric type cells, goblet cells, and occasionally Paneth cells). They occur in women in the fourth to seventh decades, are typically unilateral, and quite large (19 cm in average diameter). They are benign, provided they do not harbor foci of mucinous carcinoma (Talia 2022). They may harbor mutations in *KRAS*.

Seromucinous borderline tumors are distinguished from SBT by the presence of both serous and mucinous endocervical-like epithelial cells with abundant neutrophils, and the more frequent

association with endometriosis. Although these tumors may also be associated with peritoneal implants, no tumor-associated deaths have been reported, and the prognosis is excellent (Talia 2022).

Endometrioid borderline tumors are uncommon (Bell 2000). Up to 40% are associated with endometriosis. They may be bilateral or associated with synchronous endometrioid tumors in the endometrium and/or fallopian tube. Like their malignant counterpart, they are associated with mutations in *PTEN* and *CTTNB* (Oliva 2006) amongst others. They are benign.

## **B. Non-epithelial Ovarian Cancer**

Non-epithelial ovarian cancer consists of tumors derived from the specialized ovarian stroma (sex cord-stromal tumors) and germ cells. Sex-cord stromal neoplasms account for approximately 6% of all ovarian tumors. They contain elements of sex cord and stromal derivation, either pure or in varying combinations. The most common subtype is the fibroma. The remainder exhibit differentiation toward one or more of the following cell types: granulosa cells (most frequent) and Sertoli and/or Leydig cells (least common).

Adult granulosa cell tumor typically occurs in postmenopausal women (Li 2022). Approximately 75% are associated with estrogenic signs and/or symptoms. Adult granulosa cell tumors are unilateral and considered to be of low malignant potential. They may recur decades after diagnosis. Prognosis depends on stage of disease at presentation. They are composed of ovoid cells with euchromatic or hypochromatic nuclei, often exhibiting a “coffee bean” appearance and small, central nucleoli. The cells are arranged in a variety of patterns that vary from solid, insular and trabecular to anastomosing cords. Both macrofollicular and microfollicular (Call-Exner bodies) patterns are often emphasized, but they are absent in the majority of tumors. The microfollicular pattern is characterized by small, generally regular follicles (Call-Exner bodies). Up to 97% of adult granulosa cell tumors harbor a mutation in *FOXL2*.

Juvenile granulosa cell tumor tends to occur in children and young adults (Young 2018). Occasionally, it is seen in older women. Most, but not all juvenile granulosa cell tumors are clinically benign. They are composed of sheets or nodular aggregates of round to ovoid cells surrounding follicles that vary in size and shape and often contain eosinophilic or basophilic secretions. Call-Exner bodies are rare. They are not associated with *FOXL2* mutations.

Sertoli-Leydig cell tumors comprise less than 0.5% of ovarian tumors; they arise from Sertoli stromal cells (Young 2018). These neoplasms occur most frequently in women less than 40 years old (median 28 years old) and may present with hormonal manifestations (androgenic or estrogenic). Tumors are typically unilateral. Well differentiated tumors are considered benign tumors and are not associated with recurrence. In contrast, moderately to poorly differentiated tumors are regarded as malignant neoplasms and have a 5-year survival of approximately 78%. They have a heterogeneous morphology composed of neoplastic Sertoli cells arranged in tubules, cords, trabeculae, or sheet-like architecture and scattered Leydig cells. Heterologous differentiation, most frequently as a gastrointestinal or rhabdomyosarcomatous component may be present, but may also include chondroid, smooth muscle, or neuroendocrine, especially in the moderately and poorly differentiated tumors. The prognosis of these tumors is primarily based on grade, stage and presence of heterologous elements. Most of the moderately and poorly

differentiated tumors are associated with somatic or germline mutations in *DICER1*. *DICER1* syndrome is a rare tumor predisposition disorder associated with genetic alterations in the *DICER1* gene located on chromosome 14q32.13. This syndrome presents in children and adolescents and confers an increased lifetime risk of a variety of benign and malignant neoplasms, including tumors of the lung (pleuropulmonary blastoma), gynecologic tract, thyroid (multinodular goiter, thyroid carcinoma), kidney (cystic nephroma, Wilms' tumor), head and neck (nasal chondromesenchymal hamartoma, ciliary body medulloepithelioma), central nervous system (pituitary blastoma, pineoblastoma), and various soft tissue sarcomas (Han 2022).

Microcystic stromal tumor is a rare ovarian neoplasm that occurs in adults (Young 2018). This tumor is composed of small cells arranged in a microcystic pattern masses separated by hyaline bands and fibrous plaques. The cells express nuclear beta-catenin. These tumors harbor a mutation in *CTNGB1* and may be an extracolonic manifestation of familial adenomatous polyposis.

Steroid cell tumors comprise approximately 0.1% of ovarian tumors and are composed of large round or polyhedral steroid cells (Liu 2005). They are divided into Leydig cell tumor and steroid cell tumor not otherwise specified (NOS). Leydig cell tumors arise in the hilus or less commonly, within the ovarian stroma (Leydig cell tumor, non-hilar type) in postmenopausal women, causing hirsutism or virilization in 80% of patients. Occasionally, there are estrogenic manifestations. These tumors are associated with an excellent prognosis. On the other hand, steroid cell tumors, not otherwise specified (NOS) may occur at any age and carry a risk for metastasis. Patients frequently present with virilization due to androgen excess (41%), but occasionally with estrogenic or no endocrine manifestations. In children they may induce isosexual pseudoprecocity or result in Cushing syndrome. The tumors are almost always unilateral and FIGO stage I but 20% of patients have extraovarian extension of their tumors at the time of diagnosis.

Germ cell tumors account for approximately 30% of all ovarian tumors (Euscher 2019). Most (95%) are mature cystic teratomas (dermoid cysts). The frequency of malignant germ cell tumors is higher in countries whose populations are largely Oriental or black, in whom ovarian epithelial carcinomas are relatively uncommon. Germ cell tumors account for two-thirds of ovarian cancers during the first two decades of life.

Mature teratomas, which are almost all cystic (dermoid cysts), account for approximately 25% of all ovarian tumors. These tumors usually develop in children or reproductive age women but are sometimes not detected until years after menopause. Rarely mature teratomas are familial. Mature solid teratomas are occasionally accompanied by mature glial implants, which are almost always associated with an excellent prognosis. Monodermal teratomas include struma (thyroid), carcinoid (neuroendocrine) and strumal carcinoid (thyroid and neuroendocrine), amongst other, rarer subtypes. Mature teratomas are benign, except for those that harbor adult-type malignancies (Euscher 2019).

Immature teratomas are the third most common primitive germ cell tumors, accounting for almost 20% of all cases (Euscher 2019). They are most often found in young adults and children (median, 18 years). One-third of immature teratomas are FIGO stage II or III. These tumors are diagnosed on the basis of immature neuroectodermal elements characterized by neuroepithelial rosettes and tubules or cellular foci of mitotically active glia. Almost 90% to 100% of patients respond to combination chemotherapy with sustained remission. Mature tissue may continue to grow

(growing teratoma syndrome), requiring a second operation. Patients with exclusively mature peritoneal implants, which are composed of glia, almost always have a benign clinical course, even in the absence of postoperative treatment.

Dysgerminomas are the most common of the primitive germ cell tumors; they account for nearly half of such tumors (Warnnissorn 2021). Eighty percent of dysgerminomas develop in women younger than 30 years of age and are rare over 50 years. In patients with associated gonadoblastoma (these tumors often contain areas of calcification), an underlying abnormality in gonadal development may or may not be clinically apparent. Dysgerminomas are often unilateral and low stage. They are malignant, but respond to chemotherapy and radiation therapy with an 80% 5-year survival rate for patients with higher stage or recurrent disease. Most tumors recur within the first 2 years, but occasionally recurrence is late, even beyond 10 years. The tumor cells resemble primordial germ cells and are arranged in a predominantly diffuse or alveolar or insular pattern separated by thin to broad collagen bands infiltrated by mature lymphocytes. More than 80% of dysgerminomas show chromosome 12p abnormalities, either as i(12p) or 12p overrepresentation. Approximately one-third have *C-KIT* mutations.

Yolk sac tumors comprise about 20% of primitive germ cell tumors of the ovary (Young 2022). They occur most frequently in childhood and adolescence (mean age, 19 years). Rarely, *somatic* yolk sac tumors may be associated with endometrioid, serous, or mucinous carcinomas or carcinosarcomas in postmenopausal patients. Serum alpha fetoprotein level is almost always elevated preoperatively. This is a rapidly growing, highly malignant neoplasm, and evidence of extraovarian spread is present in approximately one-third of patients. Response to combination chemotherapy is high. The prognosis is poor when somatic yolk sac tumors are associated with an epithelial ovarian carcinoma. The tumor is composed of primitive tumor cells with clear cytoplasm (due to glycogen content and, occasionally, lipid content) and hyperchromatic, irregularly shaped large nuclei arranged in reticular, microcystic or macrocystic patterns. Schiller-Duval bodies may be present in up to 75% of cases.

### **C. Miscellaneous Tumors**

A variety of miscellaneous tumors arise in the ovary. Most notable types are small cell carcinoma, hypercalcemic type and tumors of probable Wolffian origin.

Small cell carcinoma, hypercalcemic type occurs in young females between 15 and 30 years, with a peak in the early 20s (Tischkowitz 2020). Approximately two-thirds of the tumors are associated with paraendocrine hypercalcemia. Small cell carcinomas are almost always unilateral, although involvement of the opposite ovary may be seen as part of the abdominal spread encountered at laparotomy in approximately a third of the cases. These are aggressive neoplasms with a poor prognosis, and the majority of patients die of their disease, usually within 2 years. They are composed of diffuse sheets of small, closely packed, round to occasionally spindle-shaped cells with scanty cytoplasm. Follicle-like structures lined by tumor cells are present in 80% of cases. These spaces typically contain eosinophilic, but occasionally basophilic, fluid. In 40% of tumors, a variable proportion of large cells have abundant eosinophilic cytoplasm. These tumors are associated with inactivating mutations of *SMARCA4*.

Tumors of probable Wolffian origin typically arise in the broad ligament, but may arise in the ovary (Shalaby 2020). They are composed of tumor cells that grow diffusely or form closely packed solid or hollow tubules. A sieve-like appearance is often present. The cysts contain eosinophilic luminal secretions. The tumor cells are oval or spindle shaped, and they have scanty eosinophilic cytoplasm or pale cytoplasm in solid tubular areas. They most often resemble endometrioid tumors of the ovary and are often mistaken for them. Most are benign, but occasional cases metastasize.

#### **D. Metastases**

Metastatic tumors to the ovary are common and may be misinterpreted as primary ovarian carcinomas, particularly if they arise in the gastrointestinal tract (Zhang 2020). Gastrointestinal tract primary carcinomas can exhibit features similar to primary endometrioid and mucinous adenocarcinomas and it can be difficult to distinguish them. Breast carcinoma may also metastasize to the ovaries; this can be particularly problematic in patients with *BRCA1/BRCA2* germline mutations.

In summary, ovarian carcinoma is not a single disease or even a single set of multiple diseases. The vast majority are epithelial “ovarian” cancers, but this group of tumors is composed of multiple tumor types, each with a different clinical presentation, different histopathology, different molecular pathogenesis, different disease course, and different response to various types of chemotherapy. The non-epithelial ovarian malignant tumors are similarly diverse, and there are several types of miscellaneous tumors that arise independent of both the epithelial and non-epithelial tumors. Moreover, the frequent occurrence of metastases to the ovaries and their misinterpretation as primary ovarian cancer that has historically clouded the classification of ovarian cancer continues to pose diagnostic and therapeutic difficulties to this day. Given this vast array of cancers that can occur in the ovary, it is inconceivable that any single endogenous or exogenous factor or factors can be attributed to their diverse etiologies.

### **III. TALC AND OVARIAN CANCER**

Foreign material, however inert, will evoke a response in human tissue. The initial response can be associated with acute inflammation, involving local macrophages and mast cells, and may evolve into a foreign body reaction, with formation of multinucleated foreign body giant cells and granulomas that function to wall off the foreign material from the surrounding tissue. Talc is known to elicit a foreign body reaction in human tissue (Clement 2019; Shah 2017; Irving 2015; Reichert 2012; de Brito 1994; Mostafa 1985; Perou 1973). This host response to talc is exploited in talc pleurodesis, a common FDA-approved procedure for treatment of benign and malignant pleural effusions, as well as pneumothorax. Talc is currently considered the most effective sclerosant available for pleurodesis.

**There is no correlation between the presence of talc and ovarian carcinoma.** Although the early literature hypothesized a possible role of talc in the development of ovarian cancer (e.g., Cramer 1982; Henderson 1971, 1979), subsequent accumulated data from human and animal studies have not substantiated this link (e.g., O’Brien 2020; Taher 2019; Berge 2018; Penninkilampi 2018; Visvanathan 2018; Gonzalez 2016; Houghton 2014; Terry 2013; Gates 2010; Keskin 2009; Cramer 2007; Gertig 2000; Heller 1996; Boorman 1995). Studies reporting talc

particles in cancerous and non-cancerous tissue have been cited in support of this hypothesis; however, talc (like other small mineral particulates) is relatively ubiquitous, especially in the medical profession (Heller 1996; Henderson 1971, 1979; McDonald Mar 2019; McDonald Oct 2019; Campion 2018). Talc particles identified in excised patient tissues without associated foreign body reactions are more likely than not the result of post-surgical contamination from tissue processing; such findings cannot be reliably linked to the pathogenesis of an individual patient's ovarian cancer. Indeed, if talc-related inflammation was an inciting factor in the subsequent development of ovarian HGSC, one would expect to see talc-related foreign body responses associated with the early HGSC precursor lesions (STIC) (Clement 2019; Reichert 2012; Perou 1973). This is not seen. Nor are these early STIC lesions (with the exception of intratumoral lymphocytes) associated with inflammation or with reported talc use (Malmberg 2016; Visvanathan 2018).

**Current evidence does not support chronic inflammation as a cause of ovarian cancer.**

HGSC, the most common type of ovarian cancer, is associated with STIC precursor lesions. STIC exhibits similar histologic features to that of HGSC. Both tumors may show papillary, solid, so-called pseudoendometrioid and transitional morphology. Cytological atypia is marked. Intratumoral lymphocytes may be present and can be numerous. However, there is almost never an associated chronic inflammatory process. No significant correlation has been demonstrated between HGSC and the histologic presence of chronic inflammation or chronic tubal injury (Malmberg 2016). Further, pelvic inflammatory disease, an inflammatory condition that affects the fallopian tubes and ovaries, is associated with gross and microscopic evidence of chronic inflammation and fallopian tube injury but is not reliably associated with the development of ovarian cancer (e.g., Huang 2021; Rasmussen 2017; Zhou 2017; Shen 2016). Inflammation has not been shown to be a driver of HGSC. Likewise, inflammation has not been shown to be a driver in the development of endometrioid or clear cell ovarian cancers, the next most common subtypes. Endometrioid and clear cell carcinoma are highly associated with endometriosis. Endometriosis is a multifactorial disease, and recent epidemiologic evidence suggests factors other than inflammation contribute to the development of endometriosis-associated ovarian cancers. (Huang 2021). Unlike most chronic inflammatory conditions, endometriosis-associated inflammation is hormonally driven. Defects in steroid hormone signaling contribute to the growth and survival of endometriotic tissue and these likely play a role in malignant transformation. (Bulun 2019). Several studies have demonstrated the presence of known cancer-driver mutations in uterine endometrium (*KRAS*, *PIK3CA*, *ARID1A*) that are also found in endometriotic lesions and endometriosis-associated ovarian cancers, and these likely play a role in the development of endometriosis and in ovarian cancer. (Bulun 2019). There is also some evidence to suggest that some women may have an inherited predisposition to endometriosis. (Bulun 2019). Although pelvic inflammatory disease has been tendered as a possible risk factor in ovarian cancer, the cumulative incidence rate of ovarian cancer is in fact significantly higher in patients with endometriosis than in those with pelvic inflammatory disease ( $p < 0.001$ ) (Huang 2021).

**Talc foreign body reactions are not associated with chronic, tissue destroying inflammation.**

Some chronic inflammatory conditions may be associated with risk for developing cancer. Inflammatory bowel disease (e.g., ulcerative colitis) and the development of colon cancer is one such example. Another example is that of squamous cell carcinoma arising in a chronic skin wound. Despite underlying differences in the etiology of the chronic inflammation, *each at its core is associated with histological evidence of long-term, chronic inflammation with tissue*

*destruction*. Talc foreign body reactions and granulomas are not associated with this type of chronic, tissue-destroying inflammation and have not been associated with an increased risk of cancer (Shah 2017; Hunt 2007; de Brito 1994).

**Talc particles reported in human tissue, in the absence of biological reaction, are likely lab contaminant.** Reported general findings of “birefringent” particles in tissue are irrelevant if the particles are not in the plane of section of the tissue involved by tumor, within macrophages or other cells, and/or if there is no associated inflammation or foreign body reaction in the areas or tissues in which the particles are located. Of note, many of the aggregates of birefringent material depicted in publications are sufficiently large that they would not be present in vivo without an associated foreign body response. In the absence of this expected response, one can only reasonably conclude that this material is contaminate introduced during or after surgery. If talc were present in tissue prior to resection and processing, smaller particles would be expected to be seen within macrophages, while larger particles would be expected to elicit a foreign body giant cell reaction – neither of which is demonstrated in publications. Moreover, claims in publications concerning talc in tissues of purported talc users (including some users who develop ovarian cancer) have not validated their claims with histopathologic evidence of exposure, and such findings are not consistent with my substantial experience as a gynecological pathologist and my examinations of thousands of tissue specimens from women with gynecologic cancers, including ovarian cancer.

Although publications recognize that “talc contamination of the surface of surgical pathology specimens is common,” (McDonald Mar 2019), these publications fail to recognize that laboratory processing of tissue specimens for histology can not only introduce contaminants on the surface of the specimen, but also deep within tissue (Heller 1996; McDonald Mar 2019). No published literature reports methods to adequately control for the tissue processing following surgery, making histopathologic correlation critical to support claims of biologic exposure. There are multiple steps in tissue processing following surgery that may (and often do) introduce particulate contaminate into the tissue. The fixation and processing of pathology specimens can result in introduction of foreign particulate throughout the specimen and not just on the surface of the tissue. The experienced diagnostic pathologist is well aware of the potential introduction of such material during tissue processing and refrains from issuing a diagnostic opinion in the absence of corroborating evidence of an associated cellular (i.e., presence of particulate material within macrophages with clear displacement of the macrophage cytoplasm) or foreign body reaction.

**Migration studies that claim to demonstrate that talc migrates from the perineum are not compelling.** To date, virtually all studies in humans have been based on the introduction of various materials directly into the vagina, cervical os, and/or uterus, and not on perineal exposure alone (e.g., De Boer 1972; Egli 1961; Iturralde 1981; Kunz 1996; McCalley 1985; Sjosten 2004; Ventner 1979). Aside from their questionable relevance to an individual’s use of perineal talc, these studies do not control for effects of body positioning (e.g., Trendelenberg), endogenous or exogenous exposure to oxytocin, anesthesia, or surgery (De Boer 1972; Egli 1961; Iturralde 1981; Kunz 1996; Kunz 2007; McCalley 1985; Ventner 1979). Similarly, studies that specifically utilize inert carbon particles do not control for random exposure to environmental carbon particles (Egli 1961; Wehner 1985). Also, animal studies, which are difficult to extrapolate to humans, have yielded conflicting results (Edelstam 1987; Keskin 2009; Phillips 1978; Thompson 2061). No study has provided conclusive evidence that talc, when applied to the perineum of the human female can penetrate the

cervical barrier and “migrate” to the fallopian tube and peritoneum in the absence of deliberate manipulation.

**There is also no compelling scientific evidence that talc particles in tissue cause “ovarian” cancer.** Studies reporting gene-talc interactions, immune-talc interactions, and interactions between talc and the oxidative system are largely correlative and have not been independently substantiated as bona fide mechanisms of ovarian carcinogenesis (Gates 2008; Fletcher Mar 2018; Saed 2017). The examination of cancerous and non-cancerous tissues from a patient with ovarian carcinoma with scanning electron microscopy and energy dispersive X-ray analyses is also not a sufficiently scientific or appropriate methodology for demonstrating a causal link between the presence of talc and/or asbestos and the development of the patient’s ovarian cancer (McDonald Mar 2019; McDonald Oct 2019; McDonald Nov 2019). At a minimum, a histologic response (e.g., foreign body reaction) in association with the presence of birefringent particles or the presence of particulate material within macrophages with clear displacement of the macrophage cytoplasm should be present to confirm actual exposure and to exclude artifact (e.g., Clement 2019; Reichert 2012; Perou 1973). In absence of this response, it is more likely than not that the particles are processing contaminants or “innocent bystanders.” Even in the presence of the expected histologic response, a convincing link between the presence of a foreign particle and carcinogenesis cannot be established using this methodology.

In summary, there is no scientific support to the claim that talc causes the varied and distinct diseases that are broadly referred to as “ovarian” cancer. Ovarian carcinoma is not a single disease. Although the majority are epithelial “ovarian” cancers, this diverse group of tumors is composed of multiple tumor types, each with a distinct clinical presentation, pathology, and molecular pathogenesis. No scientific study has linked talc exposure to the specific genetic alterations associated with development of all these different tumors and it is implausible that perineal exposure to talc provides a biologic mechanism for the development of these distinct diseases.

#### IV. CASE FINDINGS

In preparing my case-specific report, I reviewed the relevant medical records (e.g., operative, surgical pathology, and genetic testing reports) and available H&E stained slides from Tamara Newsome’s March 23, 2015 laparoscopic total hysterectomy, bilateral salpingo-oophorectomy, omentectomy and right pelvic lymph node dissection (S15-2514). In brief, Tamara Newsome is an African American, G3P2, with prior history of oral contraceptive use and two prior cesarean sections. At the time of her diagnosis of ovarian endometrioid carcinoma she was 53 years of age. There is no family history of other gynecological cancers. Her father had kidney/renal carcinoma at age 65 and a maternal uncle and 1<sup>st</sup> cousin had prostate cancer at 62 and 54 years, respectively. There is no history of breast cancer. The 31 H&E stained slides from her surgical procedure, which represent recuts prepared by Holy Cross Hospital, Silver Springs MD demonstrate low-grade endometrioid carcinoma (FIGO grade 1) involving the right ovary (Figure 1) and uterine serosa (Figure 2) (slides A4, A5, and A8) (FIGO stage IIA). The left ovary, right and left fallopian tubes, and omentum are uninvolved. No lymph node tissue is identified in the specimen designated as right pelvic lymph node. The carcinoma is associated with endometriosis (Figures 3 and 4) (slide A8) as well atypical endometriosis (Figures 5-7) (slides A13 and A15). Immunohistochemical stains performed on unstained slides labeled A8 in the CLIA laboratory at Stanford demonstrate the tumor cells are positive for PAX-8 (Figure 8) and cytokeratin 7 (Figure 9), but not cytokeratin

20 (Figure 10), which is compatible with ovarian endometrioid cancer (and not compatible with metastatic colorectal cancer). The tumor cells further demonstrate loss of MSH6, but not MSH2 or PMS2. CD10 highlights the stroma around the endometriotic gland (Figure 11). In addition, sections of the uterus demonstrate deep adenomyosis (Figure 12) (slides A6 and A7), cellular leiomyoma (slide A5), and benign, inactive endometrium. A *MUTYH* mutation of uncertain significance was identified on myRisk panel through Myriad.

Birefringent material is present in the slides reviewed. However, the absence of associated foreign body reaction (or even presence of particles in macrophages) identifies this material as artifact, most likely from the processing of the tissue for histology.<sup>1</sup> There is no chronic inflammation associated with the cancer.

## V. RESPONSE TO PLAINTIFF'S EXPERT

Plaintiff's pathology expert, Dr. Godleski, asserts that there is "birefringent foreign material" in 8 of the 31 slides he reviewed. The composition of this material is unknown, as it was not subjected to further analysis by Dr. Godleski. The lower two photos of Figure 1 of his report include pictures purporting to show such birefringent material in "dense collagenous stroma" and "densely cellular ovarian stroma" in areas not involved by tumor. Although he states these particles are within the plane of focus, it appears that they are overlying the tissue and not within it as he asserts. The particles are not within cells and there is no associated inflammation in these areas.

Additional photos of birefringent material were produced separate from Dr. Godleski's expert report and were also reviewed. In many of the provided pictures, it is not clear that the observed birefringent material is in the same plane of section as the tissue. There is no associated foreign body reaction in Dr. Godleski's photographs and no definitive evidence of particulate in macrophages (Godleski Report, Figure 1, and additional photomicrographs produced by Plaintiff). In addition, many of the aggregates of birefringent material depicted by Plaintiff's expert are sufficiently large that they would not be present in vivo without an associated foreign body response. As noted above, if talc were present in tissue prior to resection and processing, smaller particles would be expected to be seen within macrophages, while larger particles would be expected to elicit a foreign body giant cell reaction – neither of which is demonstrated.

Although Dr. Godleski recognizes that "talc contamination of the surface of surgical pathology specimens is common" (McDonald Mar 2019), he fails to recognize that laboratory processing of tissue specimens for histology can not only introduce contaminants on the surface of the specimen, but also deep within tissue. Despite the report's arduous description of attempts to exclude the possibility of talc contaminant, Dr. Godleski did not control for the tissue processing following surgery. There are multiple steps in tissue processing following surgery that may (and often do) introduce particulate contaminate into the tissue. The fixation and processing of pathology specimens can result in introduction of contaminants throughout the specimen and not just on the surface of the tissue. The experienced diagnostic pathologist is well aware of these potential contaminants and refrains from issuing a diagnostic opinion in the absence of associated foreign

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<sup>1</sup> To the extent asbestos is alleged to be a contaminant of talcum powder, I saw no evidence of ferruginous bodies in the available tissue to support exposure. Also, the reported association between asbestos exposure and ovarian cancer has been questioned (Slomovitz 2020; Reid 2011).

body reactions. I found no foreign body reactions supportive of talc exposure in the available slides and no evidence of particulate in macrophages.

Dr. Godleski also opines that “it can be stated to a reasonable degree of medical certainty, that the talc and tremolite asbestos found in the tissues of this case are contributory evidence for a causal link between the presence these materials and the development of this patient’s ovarian cancer.” (Godleski Report, 7). Examination of cancerous and non-cancerous tissues from a patient with endometrioid carcinoma with scanning electron microscopy and energy dispersive X-ray analyses is not a sufficiently scientific or appropriate methodology for demonstrating a causal link between the presence of talc and/or asbestos and the development of the patient’s ovarian cancer. At a minimum, a histologic response (e.g., foreign body reaction) in association with the presence of birefringent particles or the presence of particulate material within macrophages with clear displacement of the macrophage cytoplasm should be present to confirm actual exposure and to exclude artifact (e.g., Clement 2019, Reichert 2012; Perou 1973). In absence of this response, it is more likely than not that the particles are a contaminant or “innocent bystander”. Even in the presence of this histologic response, a convincing link between the presence of a foreign particle and carcinogenesis cannot be established using this methodology.

## **VI. SUMMARY OPINIONS**

There is no reliable scientific basis to conclude that talc (or any component of talcum powder) is an etiologic factor in the pathogenesis of ovarian cancer. Although several studies have reported finding talc in ovarian tissue using light microscopy and ultrastructural analysis, none has validated their claims of exposure with the known and expected histopathologic findings associated with talc. Without histopathologic correlation, laboratory contamination/artifact cannot be excluded, and this is the most likely explanation for the reported findings. Further, examination of cancerous and non-cancerous tissues from a patient with endometrioid carcinoma with scanning electron microscopy and energy dispersive X-ray analyses is not a sufficiently scientifically appropriate methodology to demonstrate a causal link between the presence of talc and the development of the patient’s ovarian cancer. The evolution of the talc-ovarian cancer hypothesis is highly reminiscent of the evolution of the (historically incorrect) hypothesis that herpes simplex virus (HSV-2), a venereal transmitted virus, was causally associated with cervical cancer. This theory was advanced largely on the basis of seroepidemiological findings (higher prevalence of HSV-2 antibodies among cancers than controls), documented HSV infection and electron microscopic evidence of viral particles in tumor tissue (Kessler 1974; Nishiura 1983; Smith 1983). Yet, extensive epidemiologic, histologic, molecular, and microviral data now demonstrate that human papilloma virus (HPV) is the causative agent for cervical cancer; this knowledge is the basis for the current HPV vaccine (Vonsky 2019). The presence of talc in tissue removed from an individual ovarian cancer patient cannot be accepted as evidence of causality *per se*. Moreover, given the vast array of cancers that can occur in the ovary, it is inconceivable that any single endogenous or exogenous factor such as talc can be attributed to their diverse etiologies.

The presence of endometriosis in tissue adjacent to Tamara Newsome's low-grade endometrioid ovarian cancer, as well as foci of atypical endometriosis that merge with the carcinoma, the additional presence of mismatch repair protein deficiency in the tumor cells and uterine adenomyosis, as well as her relatively young age at diagnosis (53 years) provide compelling

evidence that this ovarian cancer arose from endometriosis. As stated earlier in the general section of my report, endometriosis is a well-recognized precursor of ovarian endometrioid carcinoma.

**Figures**

Figure 1. Low-grade endometrioid adenocarcinoma (FIGO grade 1) involving right ovary (100x).

Figure 2. Low-grade endometrioid adenocarcinoma (FIGO grade 1) involving uterine serosa (100x).

Figure 3. Low-grade endometrioid adenocarcinoma (top) arising in right ovary associated with endometriosis (bottom left) (20x).

Figure 4. Higher magnification of endometriotic gland depicted in Figure 3 (200x).

Figure 5. Atypical endometriosis (bottom left) associated with low-grade endometrioid adenocarcinoma (top right) in right ovary (100x).

Figure 6. Higher magnification of atypical endometriosis depicted in Figure 5. The glands are complex and the epithelium is atypical (200x).

Figure 7. Another focus of atypical endometriosis exhibits cytologic atypia only (200x).

Figure 8. The adenocarcinoma exhibits strong nuclear expression for PAX-8, which is a marker for mullerian (not colorectal) differentiation (200x).

Figure 9. The adenocarcinoma also exhibits strong expression for CK7, which is also typical for mullerian differentiation (200x).

Figure 10. The adenocarcinoma is negative for CK20, which is also typical for mullerian differentiation (200x). CK20 is typically positive in colorectal adenocarcinoma.

Figure 11. CD10 highlights the stroma around the endometriotic gland depicted in Figure 4 (200x).

Figure 12. Extensive adenomyosis is present in the uterus (20x).

Newsome v. Johnson & Johnson

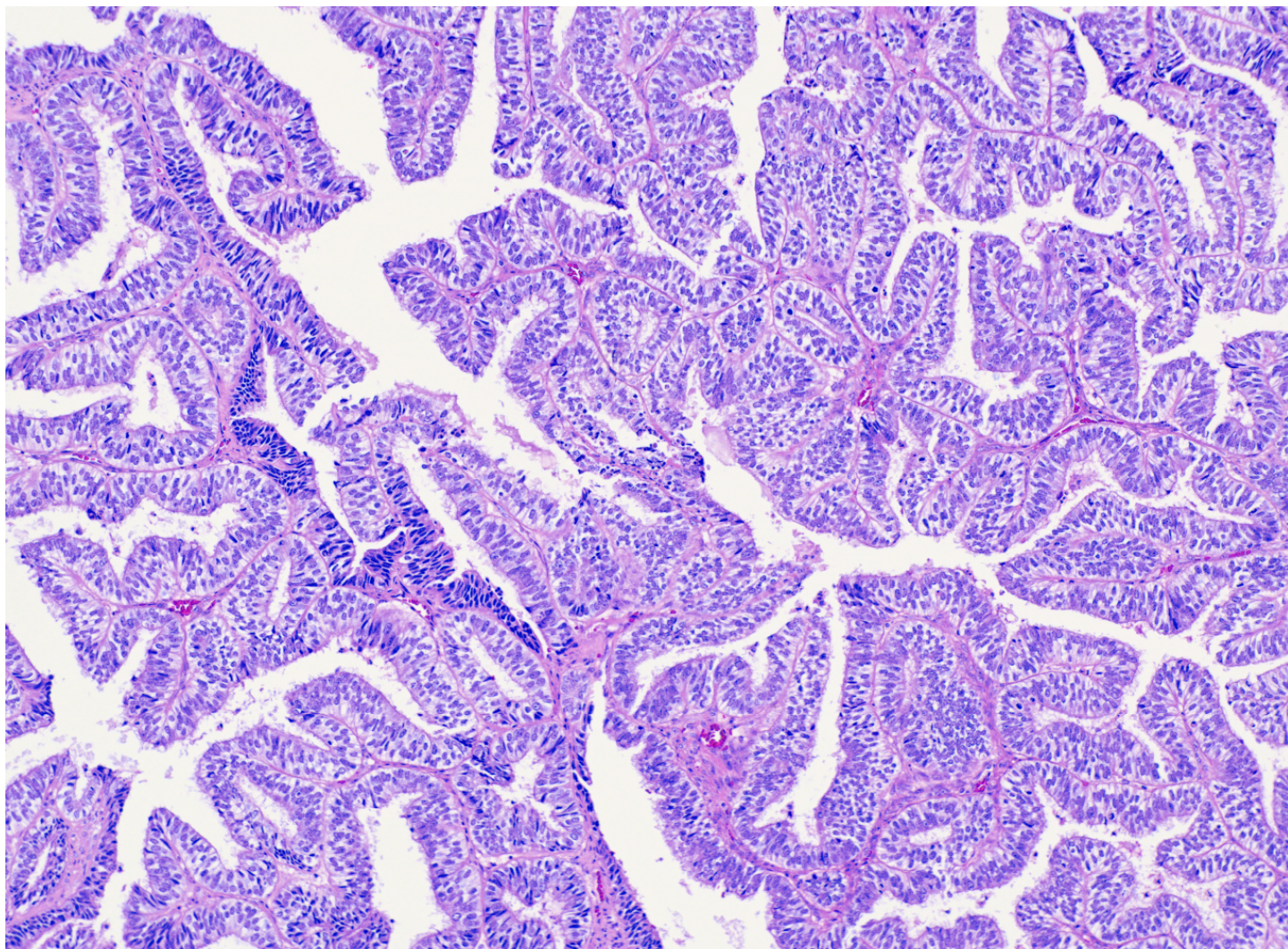


Figure 1. Low-grade endometrioid adenocarcinoma (FIGO grade 1) involving right ovary (100x).

Newsome v. Johnson & Johnson

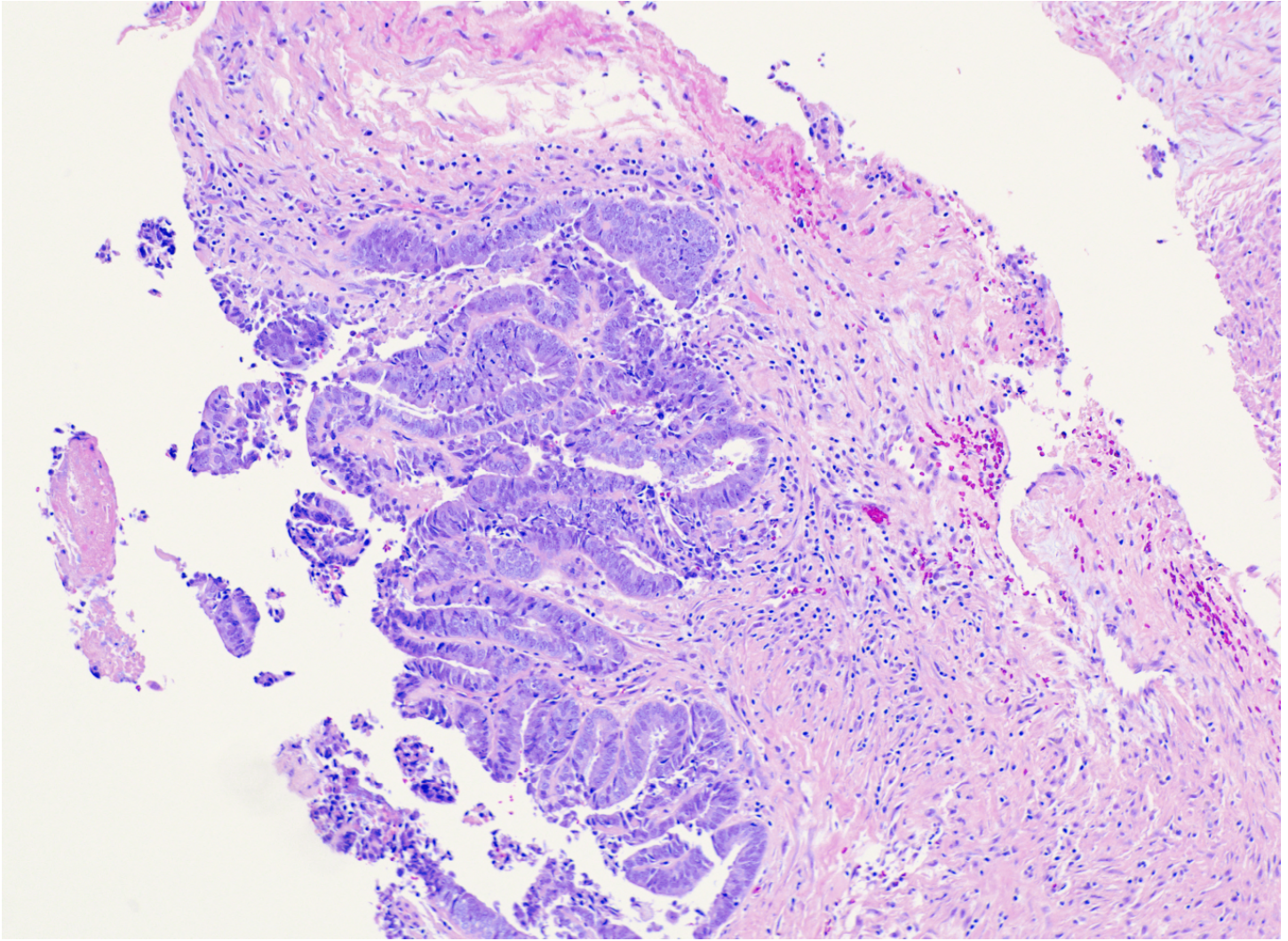


Figure 2. Low-grade endometrioid adenocarcinoma (FIGO grade 1) involving uterine serosa (100x).

Newsome v. Johnson & Johnson

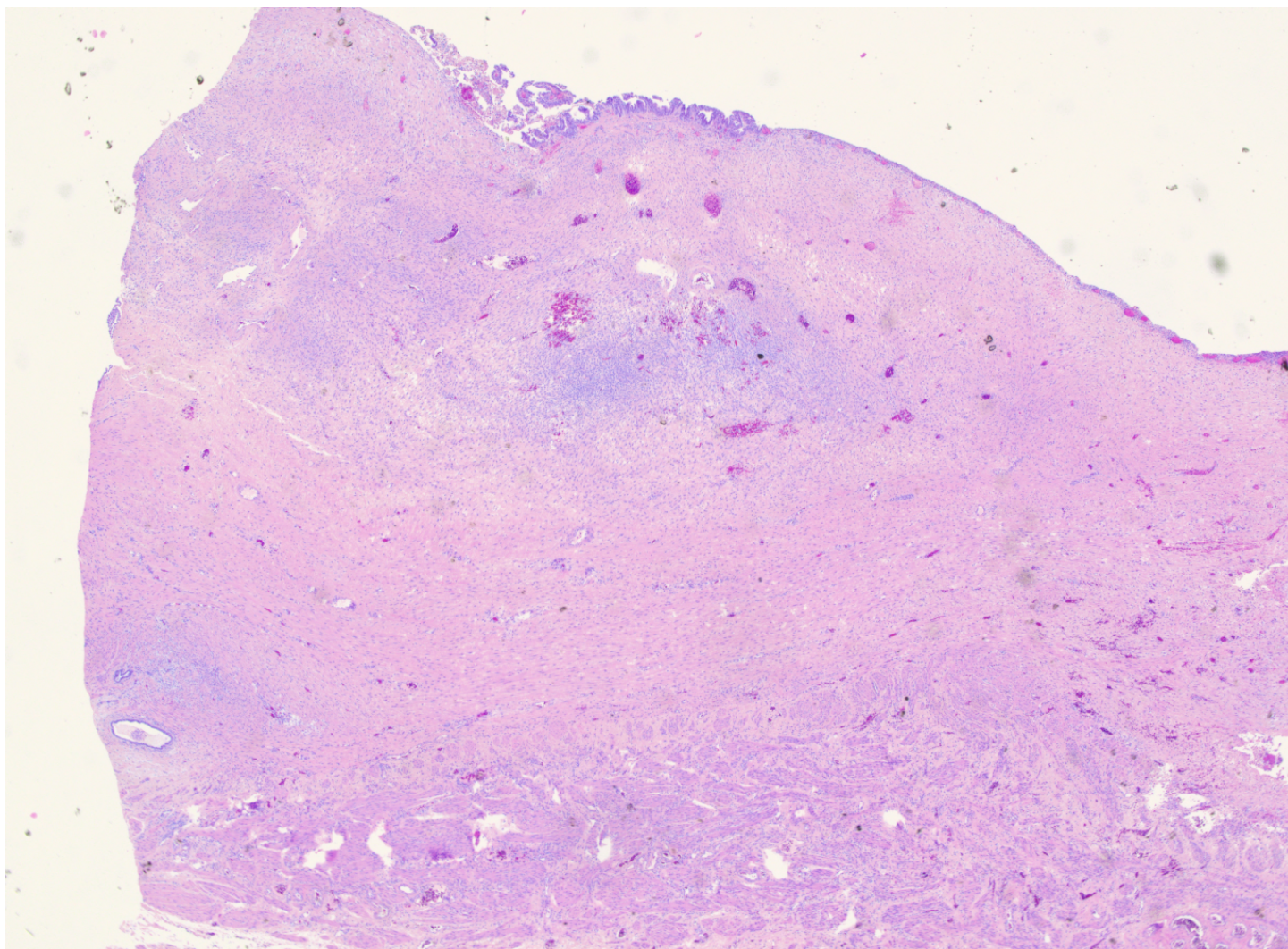


Figure 3. Low-grade endometrioid adenocarcinoma (top) arising in right ovary associated with endometriosis (bottom left) (20x).

Newsome v. Johnson & Johnson

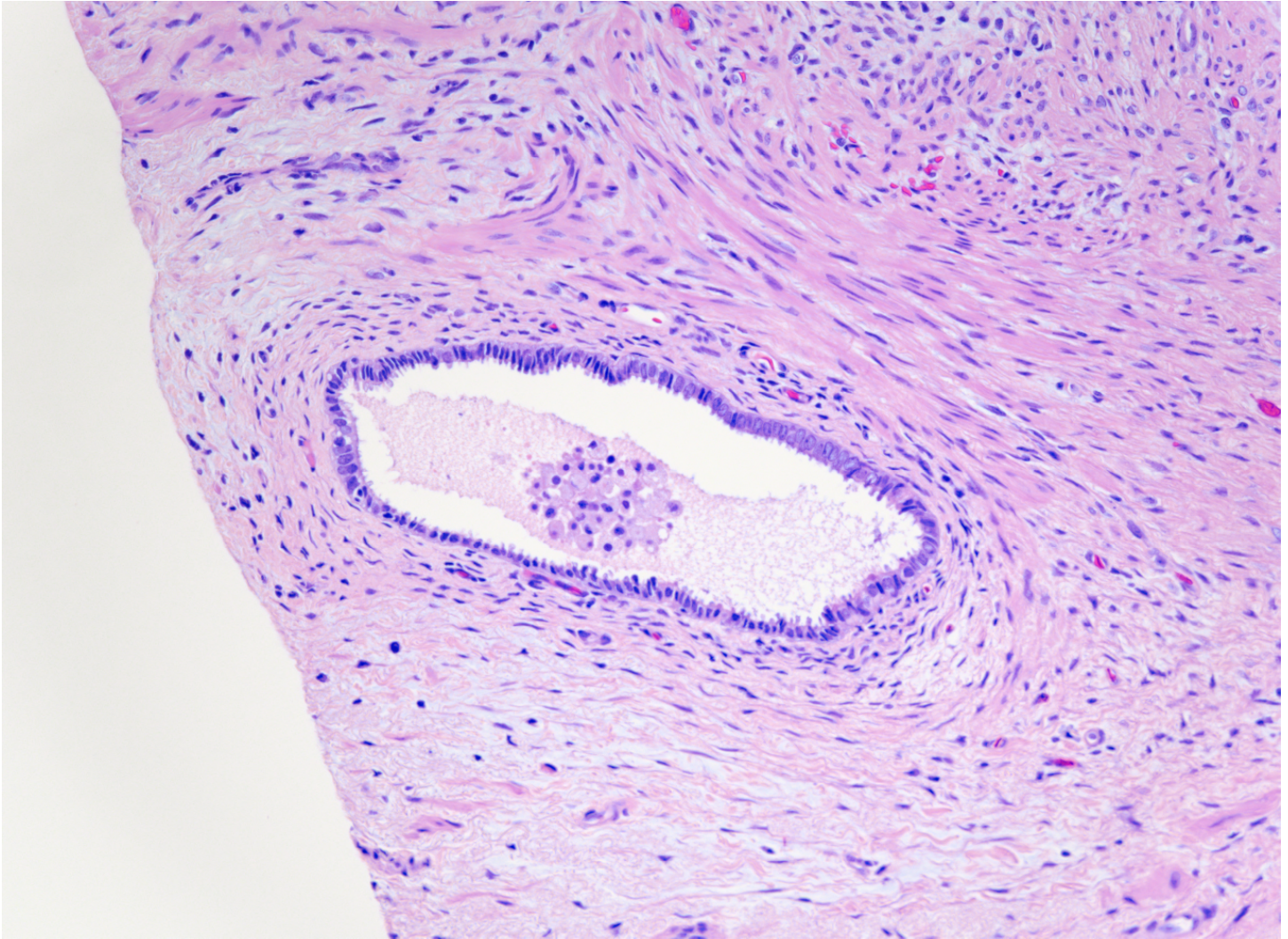


Figure 4. Higher magnification of endometriotic gland depicted in Figure 3 (200x).

Newsome v. Johnson &amp; Johnson

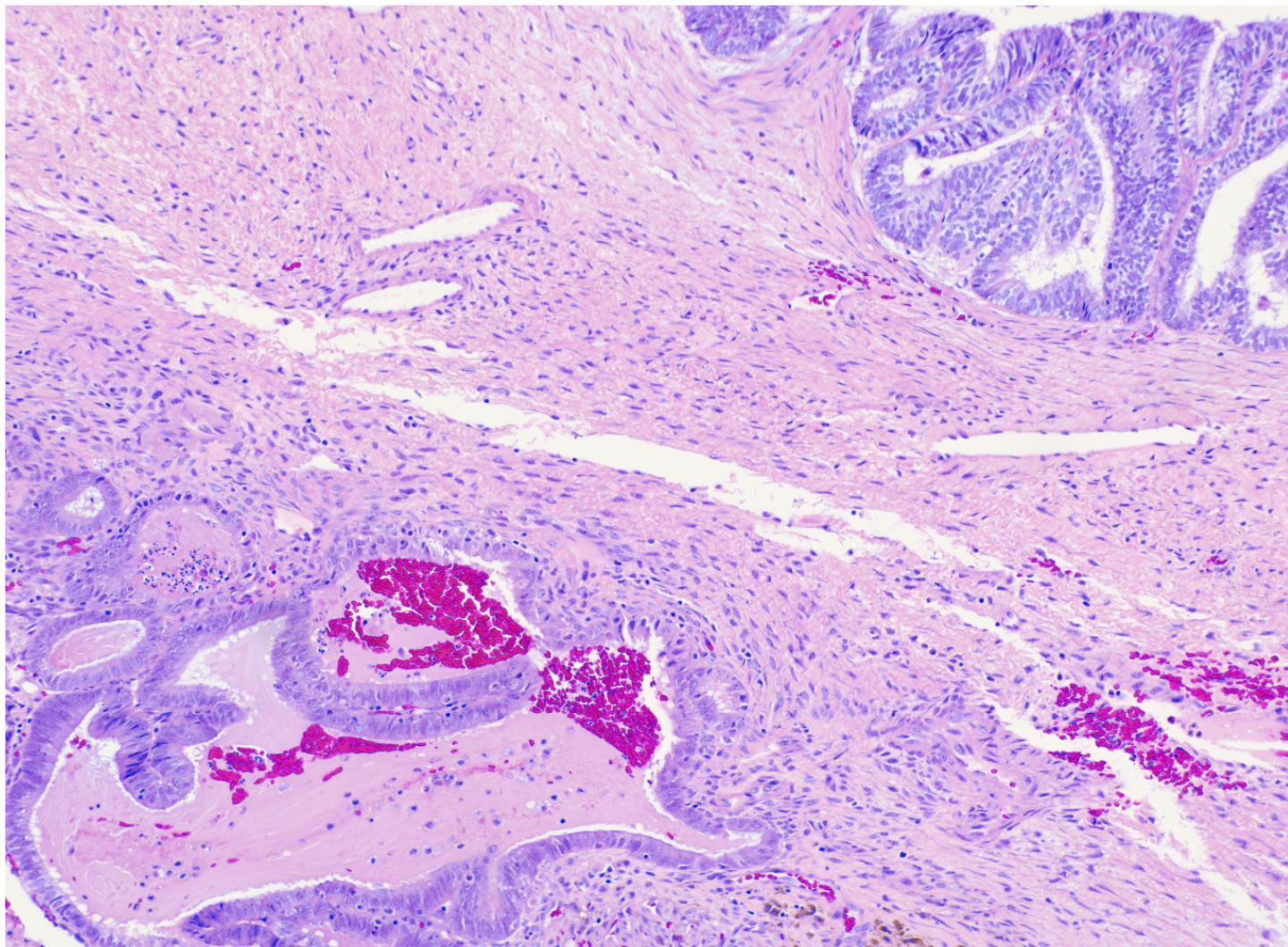


Figure 5. Atypical endometriosis (bottom left) associated with low-grade endometrioid adenocarcinoma (top right) in right ovary (100x).

Newsome v. Johnson & Johnson

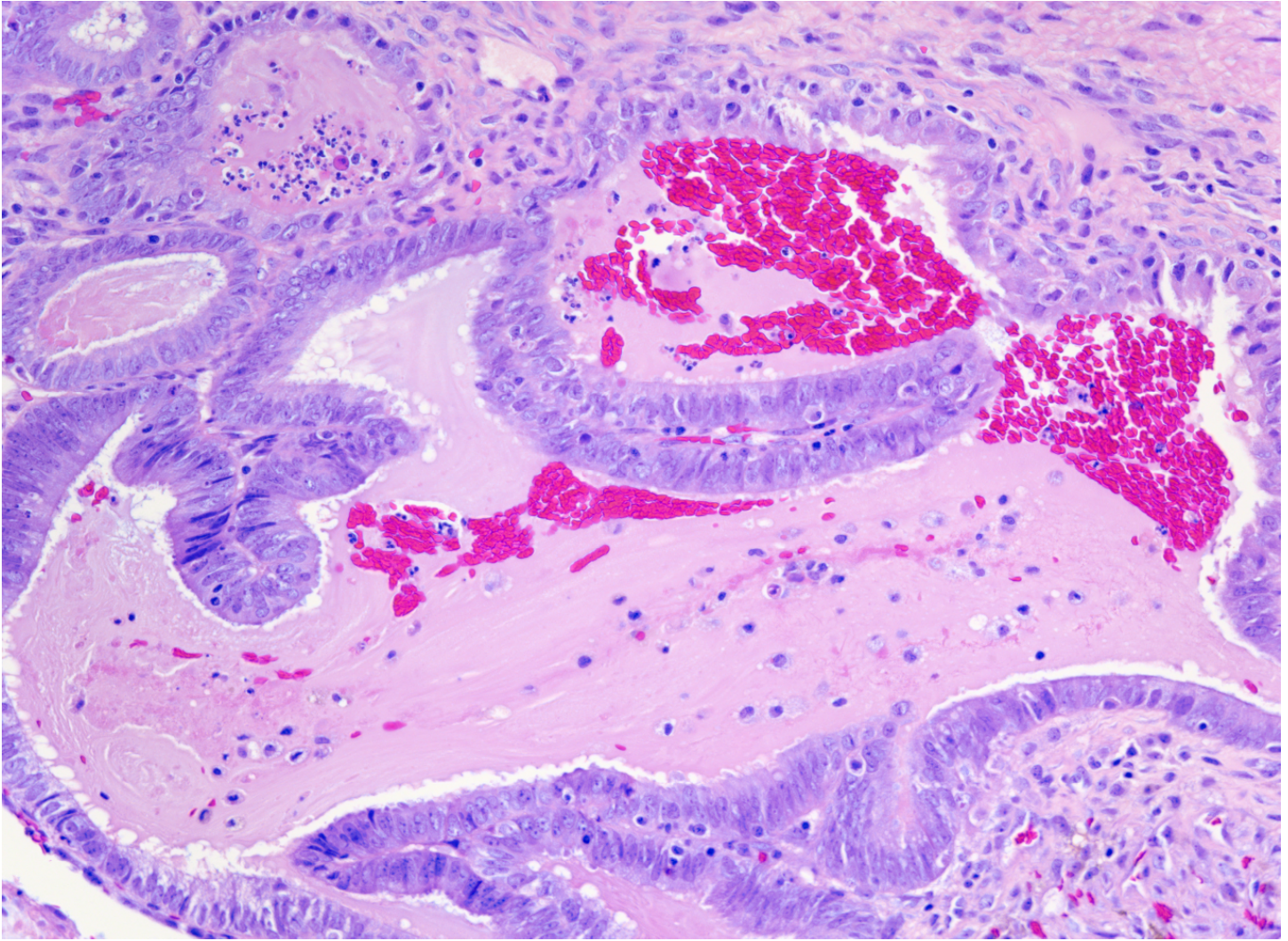


Figure 6. Higher magnification of atypical endometriosis depicted in Figure 5. The glands are complex and the epithelium is atypical (200x).

Newsome v. Johnson & Johnson

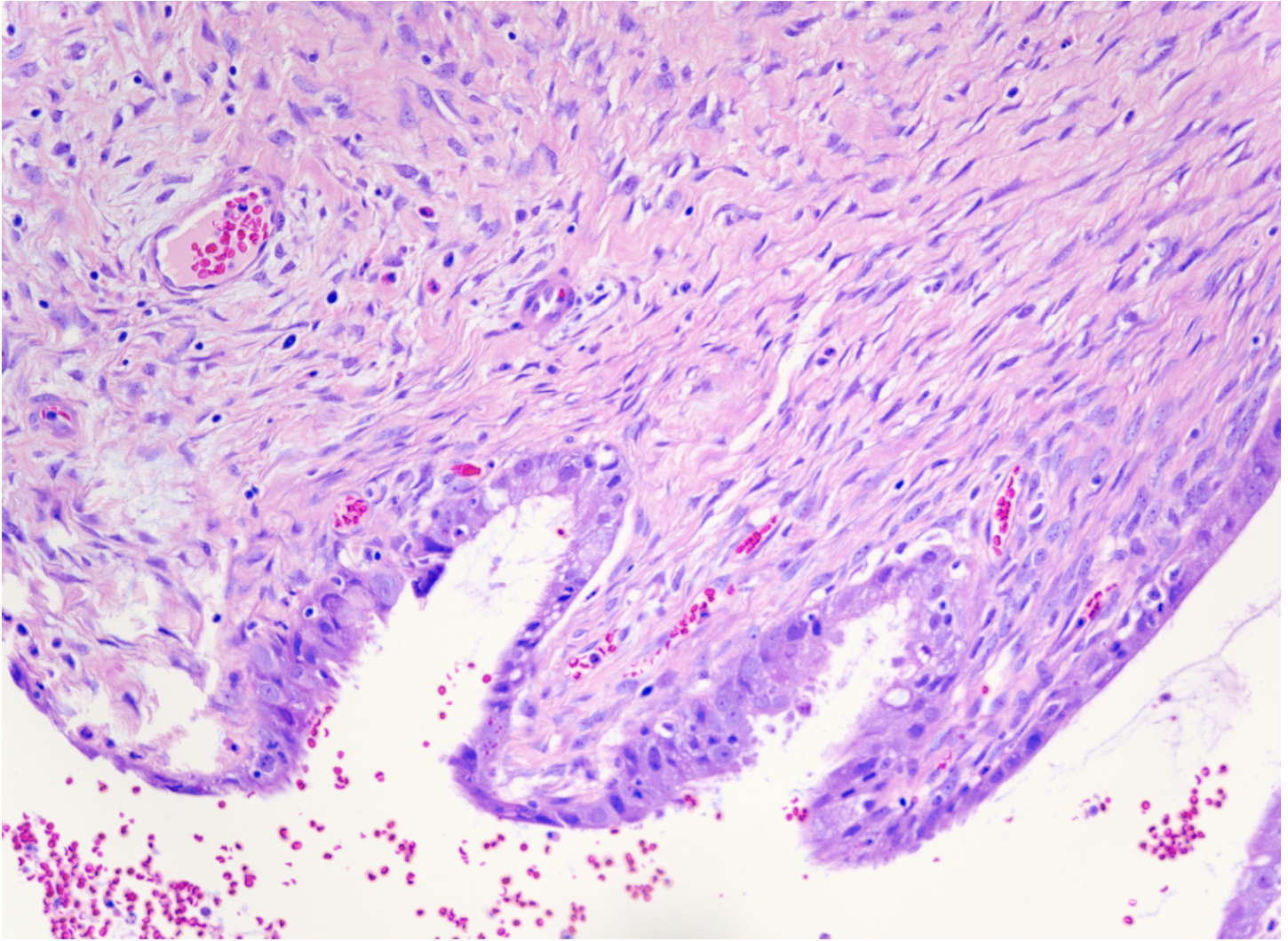


Figure 7. Another focus of atypical endometriosis exhibits cytologic atypia only (200x).

Newsome v. Johnson & Johnson

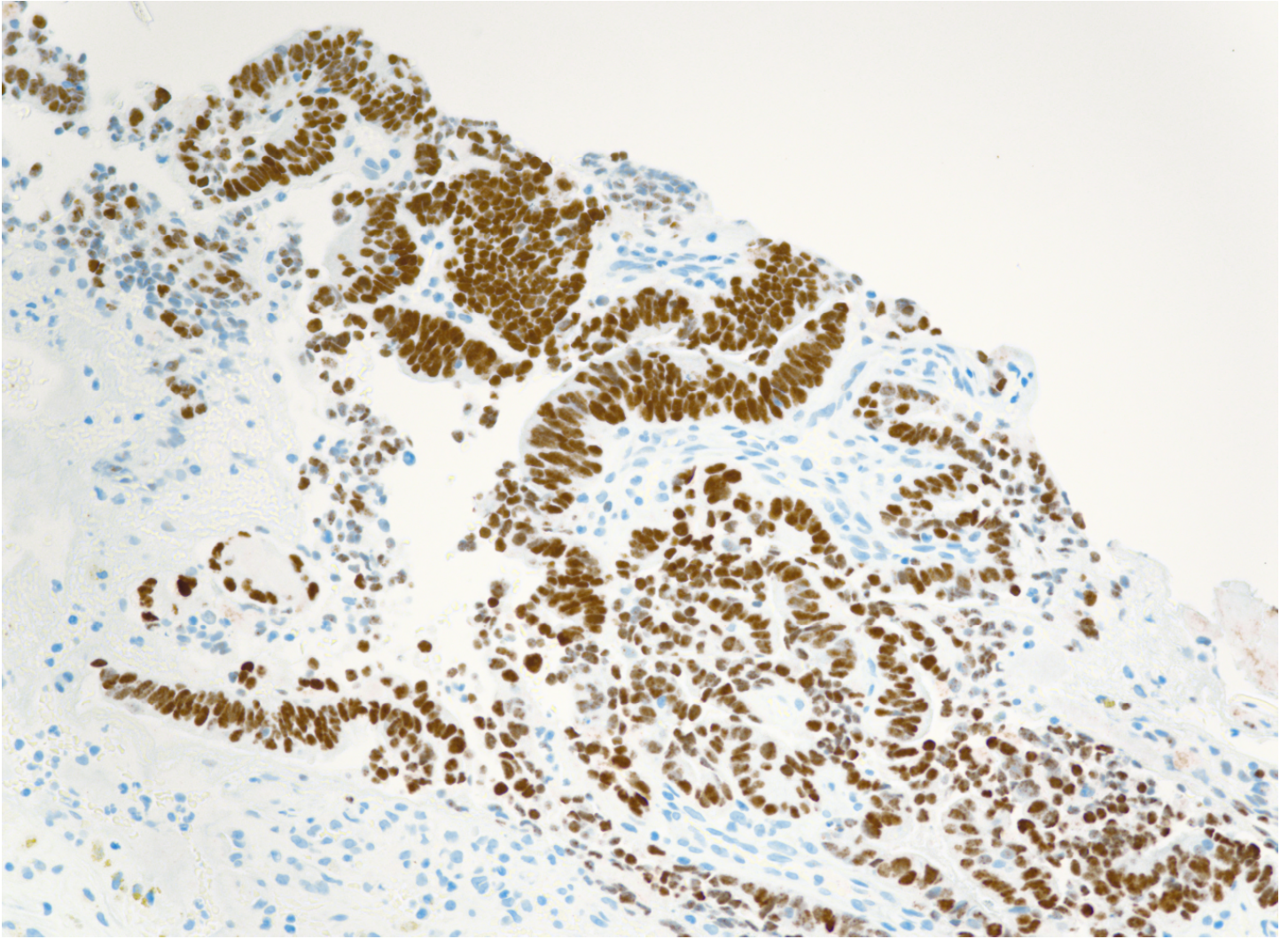


Figure 8. The adenocarcinoma exhibits strong nuclear expression for PAX-8, which is a marker for mullerian (not colorectal) differentiation (200x).

Newsome v. Johnson & Johnson

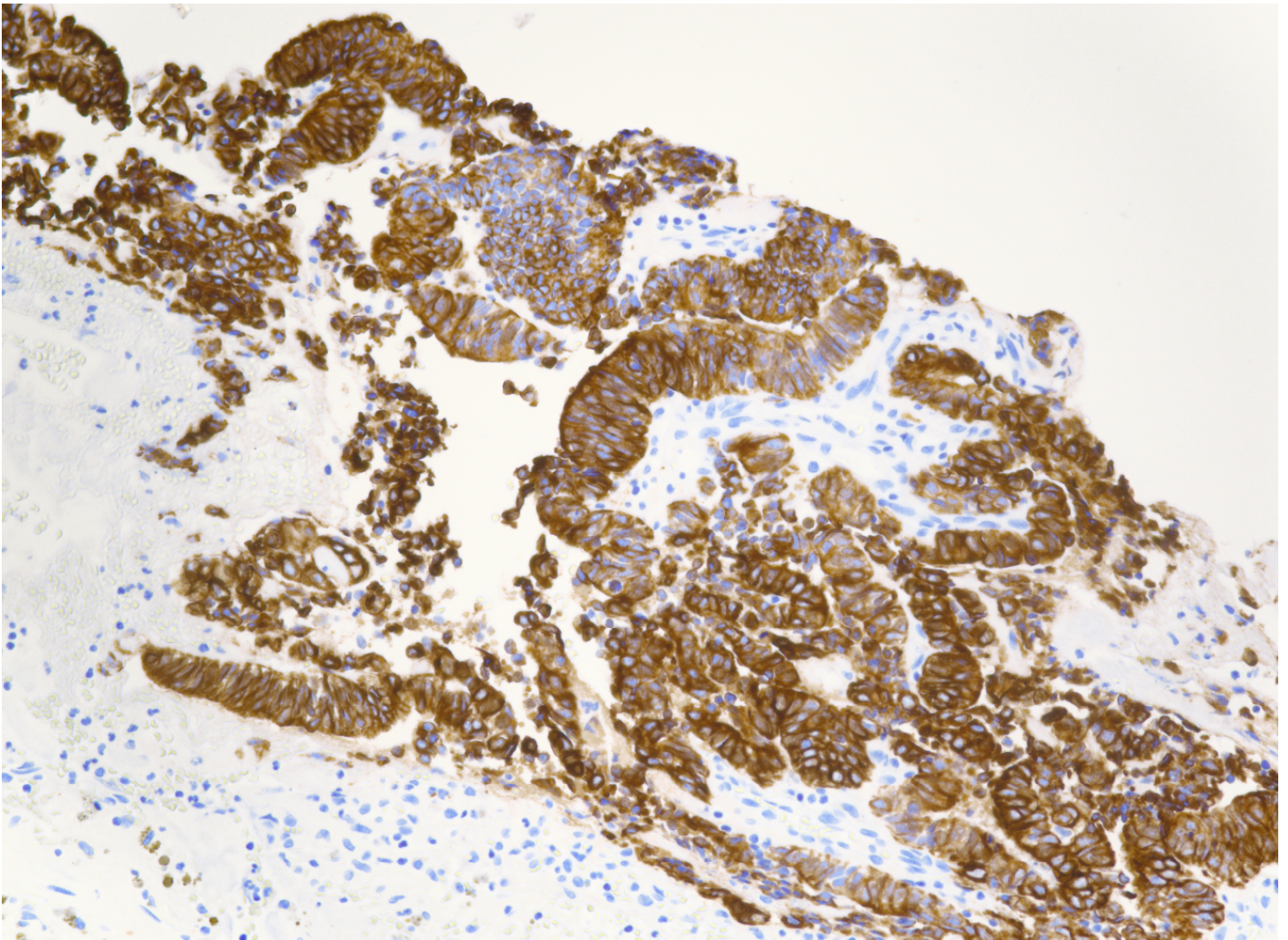


Figure 9. The adenocarcinoma also exhibits strong expression for CK7, which is also typical for mullerian differentiation (200x).

Newsome v. Johnson & Johnson

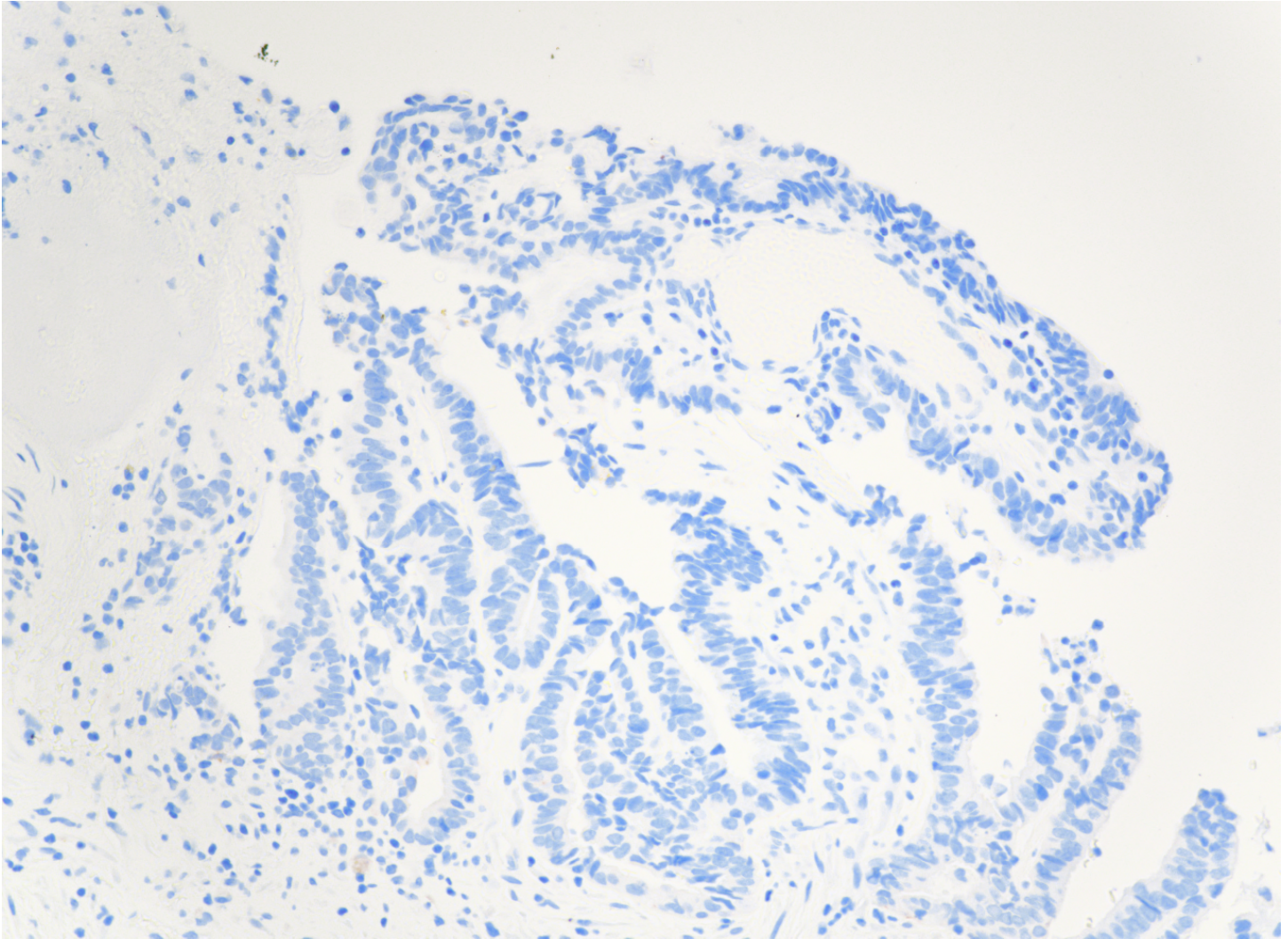


Figure 10. The adenocarcinoma is negative for CK20, which is also typical for mullerian differentiation (200x). CK20 is typically positive in colorectal adenocarcinoma.

Newsome v. Johnson & Johnson

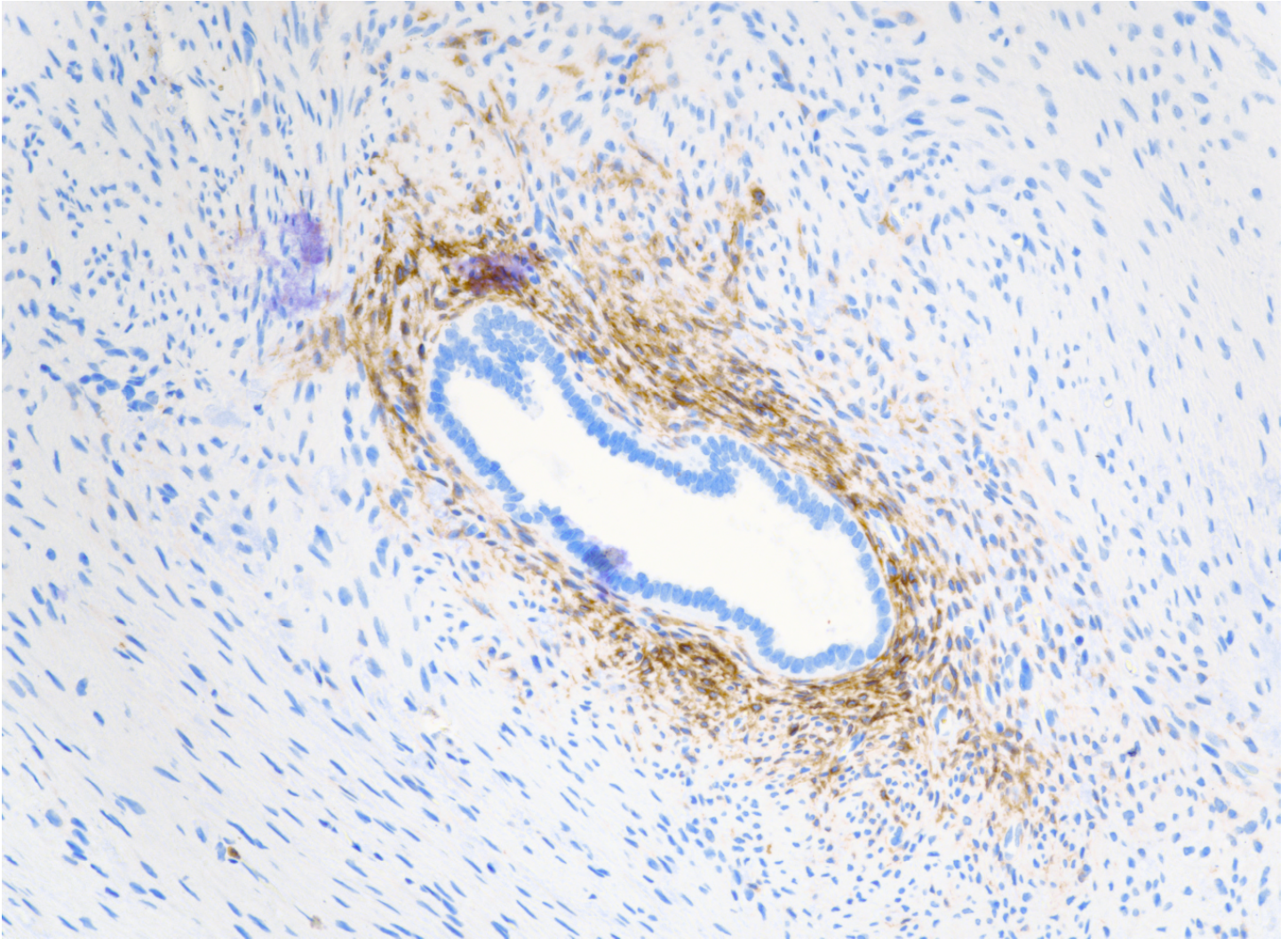


Figure 11. CD10 highlights the stroma around the endometriotic gland depicted in Figure 4 (200x).

Newsome v. Johnson & Johnson

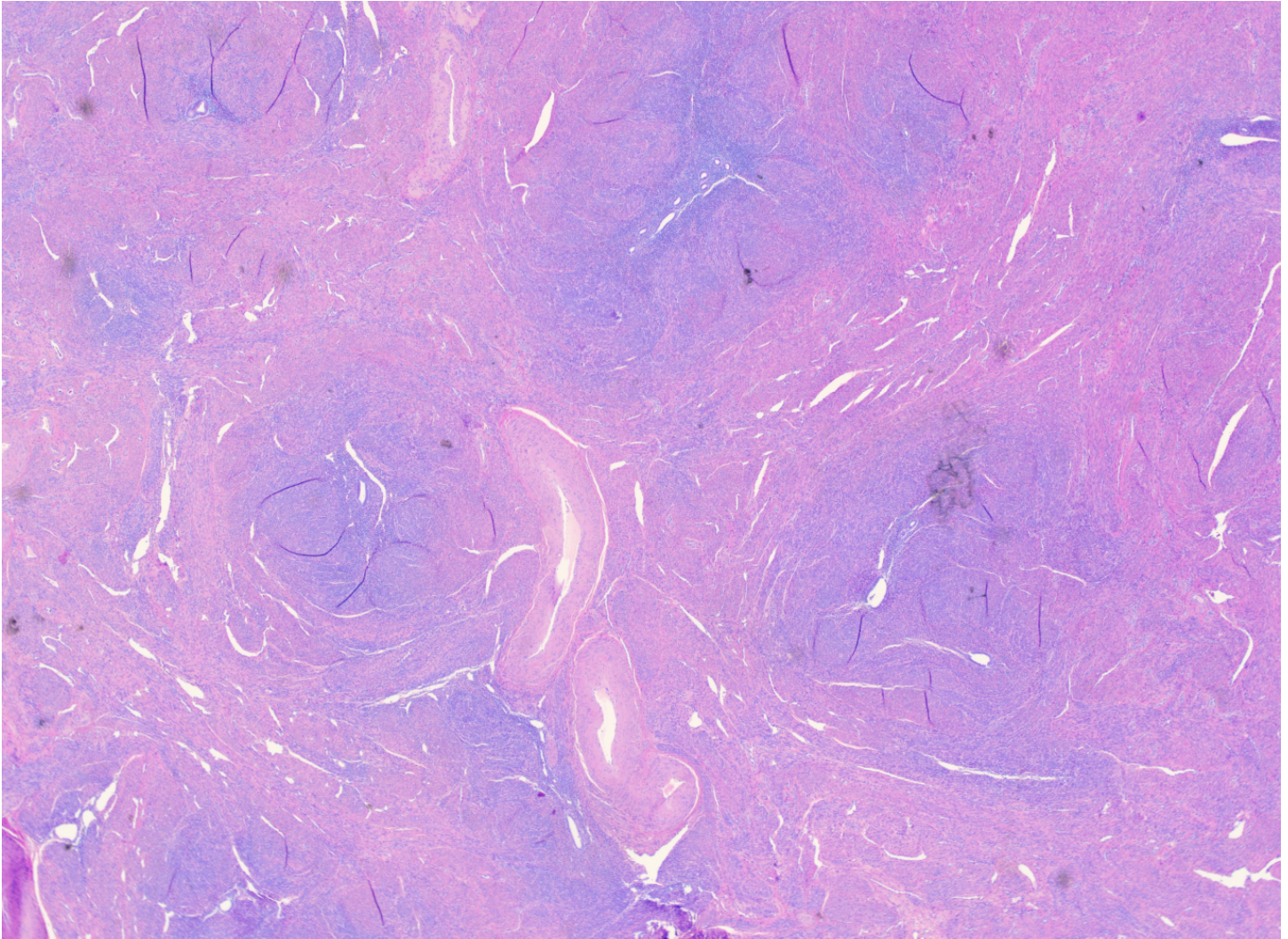


Figure 12. Extensive adenomyosis is present in the uterus (20x).